SYNOPSIS OF THE PROPOSED RESEARCH WORK

Synthesis, characterisation and analytical method development of aroma chemicals for their assay and impurity identification

SCHOOL OF CHEMICAL SCIENCE, S.R.T.M.U.,NANDED

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Synopsis

On

Synthesis, characterization and analytical method development for aroma chemicals for their assay and impurity identification.

Submitted to

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स्वामी रामानंद तीर्थ मराठवाडा विद्यापीठ, नांदेड.

For the Degree of

Doctor of Philosophy

In Chemistry

Under

Faculty of Science

By

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Research Scholar

Under the Guidance of

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Ph.D. Synopsis / Work plan
For faculty of Science to be submitted in front of RRC

Abstract of proposed work plan/ problem:

Proposed title of Ph.D. thesis: "Synthesis, characterisation and analytical method development of aroma chemicals for their assay and impurity identification"

Introduction:

Aroma chemicals means pleasant smelling compound, often are the raw materials of flavours and fragrances, the origin of aroma chemicals is from natural as well as petrochemical synthesis. The main source of aroma chemicals are isolates of essential oils i.e. from pinene (alpha & beta) which can be fractionally distilled from turpentine oil or oils from a number of species of pine it can also chemically modified i.e. alpha pinene is converted to its isomer beta-pinene and then undergoes a series of chemical reactions from which Myrcene, Linalool, Citral and many other materials are produced.

In the synthesis of petrochemicals undergo a series of chemical modifications to produce synthetic aroma chemicals e.g. Phenyl Ethyl Alcohol, Benzyl Acetate, Musk Xylol, para-Tolylaldehyde and a myriad of other aroma chemicals, some are often found in essential oils i.e. Phenyl Ethyl Alcohol in Rose, Benzyl Acetate in Jasmin and some are not found in essential oil i.e. Musk Xylol etc. The disadvantage of natural sources is variable quality, some sources non-renewable, Components responsible for interaction and changes in colour and odour hard to remove, Limited quantities get when upscaling production, Labour and land intensive, Price varies and regularly increases in comparison to synthetics other hand there are some advantage of synthetic, consistent quality, stable prices, simple clearer, controllable odours.

The Flavours and fragrances developed to enhance the demand of food, beverages, and consumer products. Generally, flavours add taste and can also provide texture to food and beverages, whereas fragrances impart desired scents to a wide range of consumer products such as soaps, perfumes, and laundry detergents etc. so its importance in global market.

Today's global competition prime focus of aroma chemical industries are to keep the cost as low as possible with sustainable process, hence in entire world aroma chemical demand growing up at highest level.

The aroma chemical molecules include most of the functional groups, from aliphatic molecules to heterocyclic ones, viz.

1. Hydrocarbons (aliphatic, acyclic terpenes, cyclic terpenes, benzenoids),

2. Alcohols (aliphatic, alicyclic, cyclic),
3. Ethers,
4. Aldehydes and ketones (including acetals and ketals),
5. Carboxylic acids,
6. Esters and lactones,
7. Nitriles,
8. Amines,
9. Nitroaromatic compounds,
10. Thio compounds,
11. Heterocyclic molecules.

Thus, to synthesis and develop analytical methods for the aroma chemical 2-phenyl ethyl alcohol and their derivatives i.e. phenyl ethyl hexanoate, phenyl ethyl cinnamate etc. by using advance synthesis techniques is prime focus. As the odour of aroma chemicals mainly depends on synthesis methodology used to manufacture of it.

2-phenyl ethyl alcohol and its derivatives are synthesis from styrene precursor by novel and sustainable way. The 2-Phenylethyl alcohol is the main component of rose oils obtained from rose blossoms, it is a colorless liquid with a mild and warm rose honey-like odor, one of the most widely used of all perfume chemicals. PEA has antimicrobial, antiseptic, and disinfectant that is used in pharmaceutics and perfumery.

2-phenyl ethyl alcohol synthesis at commercial scale reported by;

a) Friedel-Crafts alkylation of benzene using ethylene oxide and molar quantities of aluminum chloride
(b) The hydrogenation of styrene oxide.

Friedel-Crafts alkylation causes effluent disposal problems as aluminum oxychloride formed, in styrene oxide hydrogenation process used hydrogen gas along with flammable metal catalyst like Raney nickel, hence risky to handle at large scale.
So, planning to develop novel sustainable less hazardous method to synthesize 2-phenyl ethyl alcohol and their derivatives. Styrene is used as precursor as it available in market easily since it synthesized in large industrial scale from benzene.
Analytical instruments are best known for their precession and accuracy. They are mainly used to obtain valid data for research, development, manufacturing, and quality control and hence widely used in food and pharmaceutical processing machines. Much more sensitive analytical instruments are available in market but the usages of analytical instruments require procedures to train the users and to perform their assigned tasks.

Analytical instruments such as High-performance liquid chromatography, Gas chromatography, Ultraviolet-visible spectrophotometer, Ultra performance liquid chromatography etc., are widely used in research work for their high precision and accuracy. They are mainly used to obtain validate data for research, development, manufacturing and quality control.

The developed analytical method will also be validated as per ICH guidelines (Q2 R1) in terms of specificity, limit of detection (LOD), limit of quantification (LOQ), linearity, accuracy, precision solution stability and robustness.

1) Review of Literature and Development:

Literature Survey indicates that, there drastic enhancement of aroma chemical market and huge interest in the field of synthesis and their application at newly prepared fragrances and flavor has been noticed.

O. Novotny, T. Dufosse and T. Davidek[1] generated selected Maillard-derived odorants from iso-oligosaccharides, study was carried out in binary mixtures of sugar and amino acids (glycine, proline, and cysteine) and upon wafer baking. The results indicate that IOSs induce browning and generation of the majority of the monitored odorants, in particular 4-hydroxy-2,5-dimethyl-3(2H)-furanone, 2,3-butanedione, 2-acetyl-1-pyrroline, 2-propionyl-1-pyrroline, 2-acetylthiazole, and 2-acetyl-2-thiazoline, far more than the other oligosaccharides and to a higher or similar degree to that of the monosaccharides. he results indicate that IOSs induce browning and generation of the majority of the monitored odorants, in particular 4-hydroxy-2,5-dimethyl-3(2H)-furanone, 2,3-butanedione, 2- acetyl-1-pyrroline, 2-propionyl-1-pyrroline, 2-acetylthiazole, and 2-acetyl-2-thiazoline, far more than the other oligosaccharides and to a higher or similar degree to that of the monosaccharides.

A. Unuigboje and B. Emenike [2]synthesis of 2-phenylethanol was executed with bromination of benzene in the presence of pyridine to give bromobenzene which was reacted with magnesium metal to give phenylmagnesium bromide. Ethene was generated from ethanol and converted to 1,2-dibromoethane which in turn was reacted with the Grignard in an inverse manner to give 2-phenylbromoethane. Reaction of 2-phenylbromoethane and aqueous sodium hydroxide, in acetone as solvent, yielded 2-phenylethanol.

R. Kumar, P. K. Sharma, P. S. Mishra[3] summarizes the physicochemical properties, various synthetic procedures and the various pharmacological activities of vanillin derivatives, study all the vanillin derivatives showing different biological activities.

N. Masunga, B. Doyle, E. Carleschi, R. Meijboom [4] Reported good selectivity of phenyl acetaldehyde and styrene oxide by using recyclable heterogeneous manganese oxide catalyst at various reaction conditions such as solvent type, catalyst amount, styrene to TBHP ratio and temperature.

H. A. Shaaban, K. F. Mahmoud, A. A. Amin, H. A. Banna[5] presented a condensed overview of the potential offered by biocatalysts for the synthesis of natural and natural-identical odorants including flavors and fragrances, highlighting relevant biotransformation's using microorganisms and isolated enzymes.

Karl A. D. Swift[6] This book is a compilation of sixteen of the twenty papers presented at a Royal Society of Chemistry/Society of Chemical Industry Flavours and Fragrances Conference held at the University of Warwick in 2001. The chapter titles are as follows: Structure Activity Relationships and the Subjectivity of Odour Sensation (Thomas Markert); Relationships of Odour and Chemical Structure in 1- and 2-Alkyl Alcohols and Thiols (Y. Sakoda and S. Hayashi); New Developments in Sorptive Extraction for the Analysis of Flavours and Fragrances (P. Sandra, F. David, and J. Vercammen); Application of Chromatographic and Spectroscopic Methods for Solving Quality Problems in Several Flavour Aroma Chemicals (Michael Zviely et al.); Commercial Essential Oils: Truths and Consequence (Brian Lawrence); Stable Isotopes for Determining the Origin of Flavour and Fragrance Components: Recent Findings (Daniel Joulain); Fragrant Adventures in Madagascar: The Analysis of Fragrant Resin from Canarium madagascariense (Robin Clery); The Effect of Microgravity on the Fragrance of a Miniature Rose, 'Overnight Scentsation' on Space Shuttle (STS-95) (Braja D. Mookherjee, Subha Patel, and Weijia Zhou); Ambergris Fragrance Compounds from Labdanolic Acid and Larixol (Aede de Groot); The Synthesis of Fragrant Cyclopentanone Systems (Helen C. Hailes); Designing Damascone- and Ionone-like Odorants (Philip Kraft); Creation of Flavours and the Synthesis of Raw Materials Inspired by Nature (Mark L. Dewis and L. Kendrick); New Results on the Formation of Important Maillard Aroma Compounds (Peter Schieberle and Thomas Hofmann); Out of Africa: The Chemistry and Flavour Properties of the Protein Thaumatin (Steve Pearce and Hayley Roth); Stability of Thiols in an Aqueous Process Flavour (Chris Winkel et al.); and High Impact Aroma Chemicals (David J. Rowe). The book concludes with a three-page subject index.

T. Kawanobe, K. Kogami and M. Matsui [7] synthesized amber-like odorous compounds from dihydro β- and a-ionone via stereoselective acid-catalized cyc1ization of monocyclodienoic acid.

Yukio Nagasaki, Teiji Tsuruta[8] reported on a novel synthetic route for styrene derivatives having trimethylsilylmethyl groups, using the unique nucleophlic reactivity of lithium diisopropylamide toward 4-methylstyrene

Donald A. Wilson, Max L. Fletcher, and Regina M. Sullivan[9] show the critical role of acetylcholine (Ach) in olfactory system function and plasticity, and cholinergic modulation of olfactory perceptual learning at both the behavioral and cortical level.

G. Harichandran, K. Sarojini Devi1, P. Shanmugam and K. Kathiravan[10] A number of spirochromene, spiroacenaphthylene and spiro-oxindoles derivatives have been synthesized using Amberlite IRA-400 Cl resin as catalyst in water medium.

Cheng-Bin Li, Yu-Wei Li, Da-Zhen Xu[11] economical, and green strategy for the construction of biologically relevant 2-amino-4H-chromene scaffolds via a tandem Knoevenagel–Pinner cyclization–Michael reaction has been successfully developed.

T. Padte, S. Pednekar and P. Shejwalkar[12] reported Coumarins application in drug molecules especially related to oncogenic and cardiovascular dysfunctions, coumarin fragrant compounds belonging to the benzopyrone family and have been used in perfumes since five decades.

J. V. McCullagh, S. P. Hirakis[13] Synthesized Commercial Fragrance Compound Ethyl 6-Acetoxyhexanoate acid-catalyzed transesterification of the lactone.

AROMA CHEMICALS Vol.3[14] Explained importance of aroma chemicals, definition of natural, nature-identical, and artificial molecules. Synthetic ingredients play a major part as components due to their convenient availability and the relatively lower costs compared to natural molecules from isolation of relatively limited natural sources, world flavors and fragrance market data briefly presented, mentioned odor description of different aroma chemicals, written general production routes by isolation from natural source and synthesis from petrochemicals.

Cathy Galbraith Press release[15] The information contained within these reports is based upon an extensive programme of interviews throughout the industry. The reports contain market value data by product type and end-use application, with 2018 as the base year and market forecasts provided to 2023

J. Kula and J. Wilczynska[16] Described sevral aroma chemicals synthesis routes by heptaldehyde starting material namely alpha-amyl cinniamic aldehyde, Jasmone, dibydmjasmone, Methyl dihydrojasmonate, 1,3-propanediol, 1,3.butan, vinyl epoxide, dihydropyrons etc.

Xu Meng, Xiuru Bi, Chaoying Yu, Gexin Chen, Baohua Chen, Zhenqiang Jing, Peiqing Zhao[17] solvent-free ball-milling method was developed to prepare hydrophobic hydrotalcite supported Cu-Mn mixed oxide catalyst (Cu-Mn/HT).

U. Krings and R. G. Berge[18] Aroma chemicals, such as vanillin, benzaldehyde and 4-(R)-decanolide single-step biotransformations, bioconversions and de novo synthesis using microorganisms, plant cells or isolated enzymes is shown**.**
G. Centi, S. Perathoner[19] given focus on sustainable (green) chemistry by catalysis technology**.**

M. Corpet and C. Gosmini[20] new two-step procedure was developed by carbozin cation of internal and terminal alkynes to synthesise highly functionalized vinylzinc bromides. Various tri and tetrasubstituted alkenes were prepared in moderate to good yields under mild reaction conditions in a stereo-selective manner.

K. Nomura, H. Ogura, Y. Imanishi[21] presented that the Methyl phenylacetate could be efficiently hydrogenated to yield 2-phenylethanol under lower hydrogen pressure (<10 atm) by using ruthenium-phosphine catalysis composed of Ru(acac)3, P(n-C8H17)3 in the presence of Zn

Z. Khokhar, S. Munir, Sh. Asrar Ahmad, Ehsan-Ul- Haq, Aziz Ahmad Sh. Shahbaz Ali and M. A. Qadir[22] Synthesized isoamyl salicylate by reaction of isoamyl alcohol with salicylic acid using different catalysts. Sulfuric acid catalyst identified desirable, 95% yield found. Also reported the use in the preparation of beauty soap. He has done different tests for the analysis of Soap, Gas Liquid chromatography (GLC) used for purity identification.

J.E. Hayes, A.L. Jinks[23] studied effect of smoking on olfactory thresholds of phenyl ethyl alcohol and n-butanol

G. Fritter, J. A. Bajgrowicz, and P. Kraft[24] Report on fragrance chemistry summarizes the recent progress in the chemistry of important amber sandalwood, wood, musk, and floral odorants. Some details of the olfactory mechanism, current models for structore-odour relationships, and the parameters of olfactory performance are also discussed.

S. Herman[25] Explain the fragrances are the attribute of a personal care product that most affect consumers emotionally, so its commercial success corelated with emotion. Fragrances are composed of complex mixtures of natural products and aroma chemicals. Knowledge of the volatility of individual materials, and the construction of unique combinations of materials known as accords, are at the heart of fragrance creation.

Chao-Jun Li and Barry M. Trost[26] reported importance of green chemistry, Green chemistry for chemical synthesis addresses our future challenges in working with chemical processes and products by inventing novel reactions that can maximize the desired products and minimize by-products

S. Periyasamy and S. Subbiah[27] reported Green and Simple Synthesis of p-Anisic acid and Other Analogs from Methyl Paraben

M. Deshmukh, P. Anbhule, S. Jadhav, A Mali and S. Deshmukh[28] reported that phosphorus pentoxide efficient reagent for synthesis of dihydropyrimidones and its corresponding thio-analoges.

W. E. G. MuLLER, D. FALKE, B. HEICKE, and R. K. ZAHN[29] Reported that the biosynthesis of herpesvirus DNA in rabbit kidney cells is inhibited to 50% by PEA (2-Phenylethanol) at 0.65 mg PEA/ml. The inhibition of cellular DNA synthesis in uninfected cells by PEA is about twice as sensitive as that of viral DNA synthesis.

Mary Ann Liebert, Inc., Publishers[30]- Report safety assessment of phenyl ethyl alcohol, used as a fragrance and an antimicrobial preservative in cosmetic formulations. Metabolized to phenylacetic acid in mammals. In humans, it is excreted in urine as the conjugate phenylacetylglutamine. Analyzed acute, dermal and mutagenic toxicity.

S. H. Patil, K. Banerjee, S. Dasgupta, D. P. Oulkar, S. B. Patil[31] A multiresidue method is described for simultaneous estimation of 83 pesticides and 12 dioxin-like polychlorinated biphenyls (PCBs) in red and white wines

D. D. Zope, S. G. Patnekar and V. R. Kanetkar[32] developed a new synthetic method for the preparation of dihydrojasmone via a five-step synthesis from n-octanol.

T. L. White, P.Møller, E. P. Köster, H. Eichenbaum, and C. Linster[33] presented that olfactory learning and memory result from brain activity in multiple memory pathways that contribute to different strategies of memory performance. Identification of molecular and determination of assay done by validated analysis method [34]

2) Objectives of Research:

Synthesis is a scheme to generate a possible way of the desired product. It will also be called as concept design. In the design process a number of concepts will be identified and then the best concept is chosen for further development.
In flavor and fragrance industries aroma chemicals have much more significance, either it will be natural or synthetic aroma chemicals. Due to several disadvantage of natural source synthetic source plays important role in flavor and fragrance industries. Using advancement in catalysis and synthetic chemistry proposed to synthesize aroma chemicals 2-PEA from styrene and their derivatives of rose category by novel synthetic methodologies.

Objectives of research are as follows:

- To synthesize 2- PEA from styrene by simple and reliable rout.
- To synthesize 2-PEA derivatives and characterization.
- To study various application of synthesized molecule.
- To characterize synthesized molecule by easily transferable analysis methods

3) Methodology :

In the methodology of above titled synopsis synthesis of 2-phenyl ethyl alcohol from styrene and synthesis their derivatives of rose category by using novel method, develop analysis method to characterize it and study their application in perfume and flavor.

First, we synthesize the 2- phenyl ethyl alcohol, thereafter we will synthesize their derivatives which come in rose category like phenyl ethyl acetate, phenyl ethyl propionate, phenyl ethyl hexanoate, phenyl ethyl benzoate. After synthesis characterize and quantification will be done by analytical method development.

Reaction will be done batch reactors (glass round bottom flasks), condenser is utilized wherever needed, in case of higher temperature requirement it would

fulfill by applying vacuum, air and moisture sensitive reactions will be undertaken in dried glassware. Progress of reaction will be monitored using Gas chromatography

Importance of study and Application

Aroma chemicals are specifically used in a wide variety of lifestyle products. These are used to prepare fragrance formulations for consumer goods, such as perfumes, toiletries and cleaning products. As smell also affects the taste of edible goods, aroma chemicals are also used to enhance taste in processed foods and beverages. It providers are focusing on developing natural versions of synthetic flavoring agents to gain a competitive advantage in the market. The uses of Sulphur-containing molecules in fragrances have led to the creation of new compositions for fine fragrances. Globally, aroma chemical manufacturers are expected to come up with new flavours and fragrances, due to a wide range of variation options available for perfumers using sulphur-based chemicals.

Statistical data of aroma chemical market reveals that the personal expenditure increased globally on beauty and personal care products, medicines, and household care products, which is driving growth of the aroma chemicals market across the globe. Rise in population will also play a key role in increasing demand for essential consumer products, such as cleaning products and cosmetics that use aroma chemicals as ingredients. Growing awareness among consumers towards hygiene is expected to drive growth of the aroma chemicals market in the coming years.

The global market for aroma chemicals is estimated at US$4,727 million in 2018, and is forecast to grow at a CAGR of 5.3% to reach US$6,126 million by 2023.

Rose odour preferred in all categories thus proposed plan is to synthesis rose category molecule with novel and sustainable method.

Rose is the most preferred fragrance profile for skincare and soaps in India.

Aroma Chemical Market:

On the basis of application,

- Synthetic
- Natural

On the basis of chemical type,

- Terpenes
- Benzonoids

- Musk chemicals
- Others

On the basis of application,

- Fragrance
- Flavour

On the basis of functional group,

- Alcohols
- Aldehydes
- Esters
- Ketones
- Lactones
- Thiols
- Others

Region-Wise

The global aroma chemical market is segmented into the seven key regions: North America, Latin America, Western Europe, and Eastern Europe, Asia Pacific Excluding Japan (APEJ), Japan and Middle East and Africa (MEA).
APEJ is fast growing region among the rest, owing to increasing disposable income, specifically in emerging economies, such as India and China. The market for aroma chemicals in Latin America will be led by Brazil. It is projected to grow significantly due to the growing demand for cosmetics, food & beverages, and personal grooming products in the region. However, North America and Europe will hold a major share in the global aroma chemicals market, due to a huge demand for lifestyle products in the region.

Proposed work plan

The proposed work plan divided in to following five chapters

1. Introduction

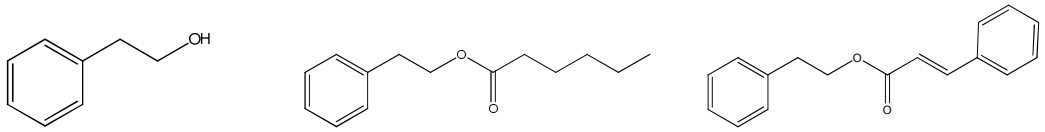
The first chapter includes the introductory part towards the point of view of aroma chemical 2-Phenyl ethyl alcohols and their application in flavor and fragrance industries.

2. Experimental techniques

This chapter describes all the solvents and chemicals used for research work and various characterization methods.

3. Synthesis of 2-PEA derivatives.

This chapter includes the synthesis of 2- PEA derivatives.



Structure of 2-PEA and their derivatives

4. Characterization of synthesized derivatives

This chapter includes the characterization and computational properties of newly designed.

5. Summery

In this chapter we will describe the summery of the thesis, like discussion, result and conclusion.

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